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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,844	05/14/2001	Yi Hu	LEX-0176-USA	8344

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EXAMINER
RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/854,844	HU ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 03 April 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *03 April 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *none*.

Claim(s) objected to: *none*.

Claim(s) rejected: *1-8*.

Claim(s) withdrawn from consideration: *none*.

8.☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☒ Other: *PTO-892*

ADVISORY ACTION

1. Claims 1-8 are pending.

2. Acknowledgment is made of Applicant's submission of a copy of the declaration containing Inventor Andrew Olson's citizenship in Paper No. 16, filed on 3/3/2003.

3. The request for consideration filed on 4/3/2003 under 37 CFR 1.116 in reply to the Final Action Paper No. 13 mailed on 12/2/2002 has been considered but is not deemed to place the application in condition for allowance for the following reasons.

4. Applicants extensively argue that the present invention has a number of substantial and credible utilities such as in diagnosis assays to detect polymorphisms at position 343 of SEQ ID NO: 1 and position 868 of SEQ ID NO: 1. Therefore, Applicants argue that the claimed polynucleotide can be used in forensics or to distinguish 50% of the population. As such, Applicants assert that there is clearly a real world, practical utility.

Applicants further argue that nucleic acids similar to those claimed are used in the biotechnology industry every day, therefore it is unclear as to how one can consider an industry which generates billions of dollars, not to be part of the "real world". Applicants argue that nucleic acids are commonly used in the manufacture of gene chips and that many patents have been issued which are related to gene chip technology. Therefore, it is Applicant's opinion that there is a "real world" substantial industrial utility for the claimed polynucleotides. In addition, Applicants indicate that a polynucleotide disclosed as GenBank accession number XM_093852 has been annotated as a serine protease by a third party not associated with Applicants and that the examples provided by the Examiner by Broun et al. (Science 282:1315-1317, 1998) and Van

de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) are hardly indicative of a high level of uncertainty in regard to predictions of function based on homology.

Applicants assert that the claimed polynucleotides have specific utility in "identification of protein coding sequence" and "mapping a unique gene to a particular chromosome", which in this case is human chromosome 4. It is Applicant's opinion that the claimed polynucleotides provide biologically validated empirical data that specifically define that portion of the corresponding genomic locus that actually encodes an exon and that such validated data is of practical scientific value. Applicants argue that while they are aware of the new Utility Guidelines, the current rules and regulations regarding patent examination are the patent laws set forth in 35 USC and the rules set forth in 37 CFR and not the MPEP or any particular guidelines. Applicants invite the Examiner to review several patents and indicate that holding the examination of their application to a different standard to that used in the examination of other patent applications would be arbitrary and capricious.

5. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the utility rejection applied to claims 1-8. In regard to forensics use, it is unclear to the Examiner as to how this can be a specific utility for the claimed polynucleotides absent an indication as to how these polymorphisms can be used to distinguish between one person from another or from one population to another. In addition, while Applicants assert that the claimed polynucleotides can be used to distinguish half of the population, the Examiner has not been able to locate any support in the specification in regard to this assertion nor can the Examiner find any information in the art in regard to how one can use these specific polymorphisms in the claimed polynucleotides as a marker to distinguish 50% of the population. In regard to "real world use",

the Examiner acknowledges that (1) the biotech industry uses polynucleotides every day in gene chips, (2) this is an industry that generates billions of dollars, and (3) many patents have been issued which are related to gene chip technology, however it is noted that it is unclear to the Examiner as to how the claimed polynucleotides in gene chips can have a "real world" utility in the absence of any information as to which is the specific biological function of the claimed polynucleotides or which are the biological process and/or conditions that correlate with the presence or absence of the claimed polynucleotides, as detected with a gene chip. One of skill in the art would require further research to determine which are the biological processes and/or conditions which are associated with the expression of the claimed polynucleotides or its specific biological function.

In regard to GenBank entry XM_093852, as indicated in previous Office Action Paper No. 13, while it is agreed that the GenBank entry submitted is highly homologous to the claimed polynucleotide, there is no evidence of its function other than being annotated as "similar" to an epidermis specific serine protease. In regard to the teachings of Broun et al. (Science 282:1315-1317, 1998) and Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995), the Examiner disagrees with Applicant's contention that these references do not support the argument that it is unpredictable to determine function based solely in structural homology. These references clearly teach that structural homologs may not be functional homologs. Furthermore, Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) as discussed in previous office action Paper No. 13 is an additional example of how two proteins having highly homologous structures (98% sequence identity) can have different functions, i.e. melamine deaminase and atrazine chlorohydrolase. In addition, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches

that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Therefore, in view of the evidence presented in regard to Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al., one of skill in the art would require some knowledge or guidance as to which are the critical structural elements required to have the desired function since, the state of the art teaches the unpredictability of assigning function based solely on structural homology.

It is noted that even if the claimed polynucleotides encode a serine protease, the specification is silent in regard to its substrate or its biological function. The art teaches that serine proteases are enzymes with a diverse function and specificity. Walker et al. (Cellular and Molecular Life Sciences, 58:596-624, 2001; page 596, first column; Abstract) teaches that serine proteases belong to a family of enzymes with an extremely diverse role in many physiological and pathological processes. Caughey (Am. R. Respir. Crit. Care Med. 150:5138-5142, 1994) teaches that serine proteases reside in all mammalian tissues and that as a group, they vary tremendously in form and target specificity, having a vast repertoire of functions (page 5138, first column; Abstract). Since neither the specification nor the art discloses the biological function or the specific substrate of the serine protease encoded by the claimed polynucleotide, further research is required to determine its specificity and its actual biological function. Therefore, the claimed polynucleotides do not have a substantial utility or a "real world" use.

In regard to arguments that the claimed polynucleotides have specific utility in "identification of protein coding sequence" and "mapping a unique gene to a particular chromosome", it is noted that any polynucleotide in human chromosome 4 can be used to identify that chromosome. Also, it is noted that while Applicants assert that the claimed

polynucleotide encodes 5 exons, no empirical determination has been made to corroborate that the claimed polynucleotide contains 5 exons. Therefore, it is unclear to the Examiner as to how the information provided by Applicants is validated empirical data or if one can use the claimed polynucleotide to map coding exons.

In regard to arguments that it is the patent laws as set forth in 35 USC and the patent rules in 37 CFR what should be used in the examination of patent applications, Applicants are reminded that the Examiner must examine a patent application according to the guidelines set forth by the USPTO as well as the MPEP, since the Examiner has no authority to disregard such guidelines or to apply her own interpretation of patent law in the examination of the application. Furthermore, as set forth in the guidelines and the MPEP, the guidelines were promulgated by the PTO in accordance with all applicable case law and thus are believed to be consistent therewith. While the Examiner acknowledges the US patents mentioned in Applicant's response, each application is examined on its own merits according to the current guidelines of examination as set forth by the USPTO and a discussion on the utility of any polynucleotide claimed in such patents would require a detailed review of the record of each individual case, which would be improper herein. Applicants are also reminded that the Examiner has no authority to comment in regard to the legality of the new utility guidelines or the MPEP as set forth by the USPTO.

6. In regard to the rejection of claim 2 under 35 USC 112, second paragraph, Applicants argue that the instant claim uses the exact language that was used in other issued US patents and that it would be arbitrary and a clear violation of due process if Applicants are hold to a different standard.

7. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the 35 USC 112, second paragraph rejection applied to claim 2. While the Examiner acknowledges the US patents mentioned by Applicants, it is noted that each application is examined on its own merits. The Examiner clearly provided the reasons why the language used was indefinite and even suggested the necessary changes in Paper No. 13. It is noted that the changes suggested by the Examiner would not have affected the scope of the claims.

8. In regard to the rejection of claims 1, 5, and 8 under 35 USC 112, first paragraph, Applicants argue that the Examiner appears to require that the function of each of the members of the genus be known in order to satisfy the written description requirement and that the Examiner has completely misread the written description requirement. Applicants argue that the teachings of Broun et al. , Van de Loo et al. and Seffernick et al. are completely irrelevant in regard to written description. Applicants argue that claim 1 provides the structural elements, specifically the nucleotide sequence itself and that there is no requirement for functional characteristics. Therefore, Applicants conclude that all that is required is the structural limitation as recited in the claim.

9. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the written description rejection of claims 1, 5 and 8 under 35 USC 112, first paragraph. As indicated previously, while it is agreed that the claimed genus of polynucleotides is defined in structural terms, the specification fails to adequately describe the genus of polynucleotides in view of the fact that there is a substantial variation within the genus due to the extremely large number of polynucleotides of any function encompassed by the claims. The teachings of Broun et al. , Van de Loo et al. and Seffernick et al. are extremely relevant since

they provide evidence that polynucleotides/polypeptides sharing common structural elements can have different functions. Witkowski et al. (Biochemistry 38:11643-11650, 1999) as discussed above, shows additional evidence in support of the argument that even if the degree of sharing of structural elements is high, i.e. only one amino acid difference, one could observe different functions. Therefore, it is unclear to the Examiner as to how one of skill in the art can reasonably conclude that the claimed polynucleotides can be adequately described if the genus encompasses polynucleotides of any function and there is only one structure and one function disclosed.

10. In regard to the enablement rejection of claims 1, 5 and 8 under 35 USC 112, first paragraph , Applicants argue that the references of Broun et al., Van de Loo et al. and Seffernick et al. are irrelevant in regard to enablement of the claimed invention. Applicants argue that a considerable amount of experimentation may be permissible if such experimentation is routine in the art. Applicants submit that significant commercial exploitation of nucleic acids do not require more information than the nucleic acid sequence itself. Applicants argue that applications such as gene expression analysis or profiling to chromosomal mapping are practiced using polynucleotides and techniques well-known in the art. It is Applicant's contention that there is sufficient knowledge and technical skill in the art for a skilled artisan to be able to make and use the claimed polynucleotides in a number of different aspects of the invention without more information than what is already provided in the specification. Applicants submit that recombinant expression, site-specific mutagenesis, in situ hybridization and large scale nucleic acid screening techniques are well known in the art. The instant rejection is improper, according to Applicants, since a patent does not need to disclose what is well known in the art.

11. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the enablement rejection. It is noted that the instant rejection was not applied because well known molecular biology techniques were not disclosed in the specification. The enablement rejection was applied in view of the fact that there is no disclosure of the functions of polynucleotides comprising at least 24 nucleotides of the polynucleotide of SEQ ID NO: 1. While one could argue that making nucleic acids as encompassed by the claims does not constitute undue experimentation since the molecular biology techniques required to make such polynucleotides are well known in the art, it is unclear to the Examiner as to how one of skill in the art can use polynucleotides for which there is no specific function disclosed. Applicants argue that for uses such as gene expression analysis, profiling or chromosomal mapping, one would not require additional information in regard to function. It is noted however that such uses are not considered patentable uses for the reasons already discussed above in regard to utility of the claimed invention. As indicated above, the teachings of Broun et al. , Van de Loo et al., Seffernick et al. and Witkowski et al. are highly relevant since they provide evidence that determining function of structural homologs using structural similarity alone is not sufficient and that one would require experimental evidence to confirm function. This would result in undue experimentation in view of the large number of polynucleotides claimed. Therefore, one cannot reasonably conclude that the specification enables the full scope of the claims.

12. The rejections previously applied to claims 1-8 are, therefore, maintained for the reasons of record.

13. For purposes of Appeal, the status of the claims is as follows:

Claim(s) allowed: NONE

Claims(s) objected to: NONE

Claim(s) rejected: 1-8

Claim(s) withdrawn from consideration: NONE

14. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
April 24, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1300~~ 1600